TRANSLATION NO. 2282

DATE: Aug 1968

DDC AVAILABILITY NOTICE

This document has been approved for public release and sale; its distribution is unlimited.

DEPARTMENT OF THE ARMY
Fort Detrick
Frederick, Maryland

T-646-4

2282

THE PROBLEM OF TUMOR VIRUSES AT THE IXth INTERNATIONAL CONGRESS OF MICROBIOLOGISTS

[Following is the translation of an article by V. Ya. Shevlyagin, published in the Russian-language periodical Voprosy Virusologii (Problems of Virology), No 3, 1967, pages 376-379.]

Out of all the reports which were presented at the congress, which dealt with tumor viruses, the most important ones were separated into a special discussion (in other words a symposium). The most interesting fact which was discovered in recent years during the study of tumor viruses is probably connected with hybrids of the SV_{40} virus with adenoviruses. This problem was dealt with in the report by Melnik and Rapp (USA), who studied the SV_{40} hybrid with adenovirus type 7. This hybrid is capable of inducing the synthesis of tumorous T-antigen, which is characteristic for the SV_{40} virus, in various cell cultures, but does not induce the viral antigen which is characteristic for SV_{40} virus in one of the tested cultures. In newborn hamsters the hybrid causes tumors containing the T-antigen which is characteristic for the SV_{40} virus. The hybrid includes not only genetic information, responsible for the induction of intranuclear tumorous T-antigen, but also information which specifies the appearance of transplantation resistance. It was revealed that a hybrid population consists of 2 types of virus particles: the 1st is an adenovirion, devoid of the SV_{40} determinant, and the 2nd is a virion having the SV_{40} determinant in the capsids of the adenovirus. Both types of particles are necessary for the prolonged multiplication of the hybrid population.

Deynkhardt (USA) reported about useing marmosets for obtaining tumors in them under the influence of Rous virus. These monkeys are somewhat larger in size than squirrels and can multiply under ordinary laboratory conditions. Five monkeys which were born in captivity were inoculated subcutaneously and intramuscularly during the first 24 hours of life with cell-less preparations of Rous virus (Schmidt-Ruppin strain). In all the marmosets invasive metastatic immature sarcomas developed between the 20th and 90th day after inoculation. The monkeys died from malignant neoplasms between the 55th and 117th day. Live tumorous cells from one of these animals were inoculated into its 30-day old twins and in two weeks large sarcomas developed at the site of inoculation. This model of primary viral tumors of mammals is probably the closest to primary tumors of man and is easily reproduced in laboratory animals.

Rich (USA) came forward with an extensive and thorough report

dealing with the immunological differentiation of various viruses of mouse leukemia.

Evans and Ito (USA) devoted their report to the study of the Shaup papilloma virus. Preparations of DNA, isolated from the papilloma virus, caused the formation of papillomas in rabbits with papillomas or carcinomas which were already growing. At the same time preparations of virus DNA could not cause the formation of papillomas in one of the 15 rabbits in which papillomas dissipated 6-15 weeks prior to this.

There was a great deal of interest in the work by Svoboda (Czechoslovakia) on the study of mammal cells which had been transformed by the Rous virus. Very often these cells contain the so-called virus which is intimately bound with the cells. It could be detected only following the administration of whole cells to chicks or following the joint cultivation of tumor cells in vitro with cells of chick embryos. The virus was not contained either in extracts or in filtrates prepared from tumorous cells alone. Also it could not be activated by any of the known chemical or physical methods. An analysis of a population of tumorous cells which contained this virus was dealt with in an address by Svoboda at a special discussion.

Of the reports which were presented at the 2 sectional conferences it is necessary to give primary attention to the papers on the study of the interrelationship between the genetic apparatus of viruses with the genetic apparatus of cells. It is doubtless that the mechanism of the transformation of a normal cell into a tumorous one will be resolved primarily by a study of these questions. Unfortunately there are very few of these works. Sheypin (Canada) demonstrated that in embryonic cells of rats which were infected with the polyoma virus inhibition of cellular DNA was not detected as this was demonstrated in a number of other investigations. Also in her tests it was noted that there was even a certain intensification of synthesis of cellular nucleic acids under the influence of the polyoma virus.

Ben-Porat, Tennant, and Kaplan (USA) presented evidence that cellular RNA of the host takes part in the synthesis of polyoma virus. It is interesting that in the process of synthesis of another virus, also containing DNA but not causing tumors - the virus of pseudorabies - cellular RNA does not take part.

In the embryonic cells of mice and chickens N. D. Nadgornaya, A. M. Shcherbinskaya, and M. I. Milon' (USSR) studied changes in nucleic metabolism and the activity of certain enzymes in the process of infection of these cells with the virus of polyoma, Rous sarcoma, and mouse leukemia (Mazurenko strain). In the period of absorption of viruses on the cells an increase was noted in the content of nucleic acids in the cells, then (in the first days of infection) a lowering, and in 5-6 days again an increase in the content of cellular nucleic acids. In subsequent days the quantity

of nucleic acids in the cells was reduced, but in cultural medium it increased.

In 2 papers new data were presented on the transformation of tumorous viruses of cells in vitro. V. Ya. Shovlyagin and [illegible] (USSR) demonstrated the feasibility of the transformation of human embryonic musculocutaneous tissue of man by the Karra-Silber strain of the Rous sarcoma virus. Tindol, Titer, Otten, Bowles, and Apton (USA) reported on the results of experiments on the transformation of cells of the transplanted BALB/C strain of mice by the virus of Rausher leukemia. Soon after infection the cells changed their morphology and began to form three-dimensional accumulations. Following subcutaneous administration of the transformed cells to newborn BALB/C mice myxofibrosarcomas developed at the site of administration.

Several works dealt with the study of immunity to tumors which are caused by viruses, and also the use of viruses for the suppression of the development of tumors.

In a detailed report G. I. Deychman and T. Ye. Klyucharева (USSR) reported on the effectiveness and limitations of the application of specific prophylaxis of tumors in golden hamsters which were caused by the SV_{40} virus. Those animals, inoculated in a newborn state with the SV_{40} virus could subsequently, in the course of the latent period, be vaccinated with preparations of live virus or irradiated tumorous cells. It was shown in the work that the most effective is the vaccination of the animals as early as possible, and later vaccination (1-2 weeks prior to the appearance of the tumors) generally does not influence the appearance of neoplasms. Moreover in tumors which developed in animals which were vaccinated in the late latent period there was observed a disappearance of specific tumorous antigen. This was ascertained in the reaction of transplantation resistance.

This same problem was studied by Eddy, Crabe, and Yang (USA). In their experiments they also showed the feasibility of causing immunity in golden hamsters which were infected with SV_{40} viruses or adenovirus type 12. The repeated administration of doses of viruses to the animals in the latent period was accompanied by their development of an immunity to tumors. This immunity was specific: tumors did not develop only when the animals received during the latent period the same virus with which they were infected initially.

V. P. Gamburg, A. L. Liozner, and G. Ya. Svet-Moldavskiy (USSR) reported on the results of experiments on the interaction of tumorous viruses with cells of various tumors which were caused by various chemical carcinogens. Earlier these investigators demonstrated that following infection of already formed tumorous cells with various tumorous viruses antigens which were specific for the given viruses developed in the tumorous cells. This phenomenon was called "artificial heterogenization of a tumor."

The growth of such tumors is specifically suppressed in animals which had been immunized with this tumorous virus. In a report presented at the congress data were presented which broadened our proposal about the interaction of tumor viruses with tumorous cells. Thus in golden hamsters with tumors caused by 7,12 dibenzanthracene and "heterogenized" by SV_{40} virus an accelerated growth of these neoplasms was noted. If this tumor was used to inoculate animals which had been previously immunized with the SV_{40} virus then the growth of tumors is suppressed. It turned out that it was also possible to obtain artificial heterogenization of tumors at the moment of their formation during chemical cancerogenesis. A doubtless oncolytic activity was noted in the in vitro experiments with adenovirus type 16.

A. Ya. Muntseniek and I. D. Chernobayeva (USSR) studied the behavior of enteroviruses which were administered to rats, mice, and golden hamsters with transplanted homologous and heterologous tumors. Evidence was obtained of the selective multiplication of some of the virus strains studied in tumors in which in a number of cases was accompanied by a significant destruction of tumorous tissue. However this destruction lasted no later than the 4-6th day following administration of viruses, which may be connected with the formation of an immune reaction to the virus. It is interesting that attenuation of viruses does not impede their capacity to be selectively localized in tumors and to destroy cancerous cells. Also chemotherapeutic antitumerous compounds do not prevent fixation of the virus in tumors, but these preparations may contribute to the generalization of viral infection.

Iton (USA) showed that the administration of cells of mouse lymphoma together with the virus of Newcastle disease increases the resistance of animals to this tumor.

All of the subsequent papers were devoted mainly to a study of some biological properties of tumorous viruses.

V. N. Stepina, R. P. Dirlugyan, and N. P. Mazurenko (USSR) studied various viruses of mouse leukemia in the reactions of transplantation resistance, immunofluorescence, and neutralization. The authors established a closeness between the viruses of Frend and Mazurenko leukemia in an antigenic respect.

Z. A. Butenko and Ya. I. Morgunova (USSR) reported on the detection of a leukogenic and oncogenic effect by general high-polymeric cytoplasmic RNA which was isolated from leukemic tissue of rats. The stated activity was manifested only following the administration of preparations of RNA to newborn rats. These same preparations possessed a cytopathic activity in rat embryonic tissue in vitro. Both of the described phenomena were removed by the action of ribonuclease on preparations of RNA.

Pandos, Molomat, and Satori (USA) investigated the biological

peculiarities of lymphocytopenic virus which reduced the amount of lymphocytes in the peripheral blood in mice, rats, kittens, and puppies, and also caused a reduction in the number of lymphocytes in the spleen, thymus, and lymph nodes of mice. The physical and chemical peculiarities of this agent were studied and the differences between it and the viruses of mouse leukemia of the Molon, Rausher, and Frend strains and the LCM virus were shown.

Pasternak (GDR) discussed experiments on the further study of the properties of the Grafi virus of mouse leukemia.

Medyalkov (Bulgaria) studied the biological properties of the virus of chick myelocytosis (strain Mc-31). This virus caused leukemia not only in young chickens but also in turkey chicks. At the same time it was inactive in ducklings, goslings, and in newborn mice, rats, guinea pigs, rabbits, and hamsters.

A. T. Kravchenko, A. D. Al'tshteyn, Ye. S. Voronin, Ye. A. Shchekochikhina, and G. L. Ryazanova (USSR) made a comparative study of the properties of several strains of the Rous sarcoma virus. In experiments a correlation was noted between the capacity of certain strains of Rous sarcoma to form large spots on chorio-allantoic membranes of chick embryos and a higher degree of oncogenicity of the Brayan strain for young chicks. This strain of virus did not cause tumors in golden hamsters.

At the same time the Karr-Zil'bar and Shmidt-Ruppin strains, which were less active on young chickens, easily caused tumors in mammals. All the strains of Rous virus were clearly distinguished in the neutralization reaction.

In experiments by V. A. Parnes and D. M. Levina (USSR) the virus of erythroblastosis (strain R) caused tumors and cysts in a significant percentage of rats of the Vistar line. Viral antigen was detected in cells of these tumors and also in liver cells from rats with tumors. The virus under study was inactive when administered to 5 lines of mice.

Ye. Ye. Pogosyants, R. M. Radzikhovskaya, and E. T. Bruyanko (USSR) in their investigations used steppe rainbow trout (Lagurus lagurus) for obtaining tumors under the influence of the Rous virus. The average latent period for the appearance of tumors was from 29 to 43 days (for various age groups). In all cases numerous sarcomas were recorded which caused the death of the animals.

R. I. Rappoport, E. E. Rozina, A. N. Avakova, and O. G. Andzhaparidze (USSR) studied morphological criteria of tumorogeneity of various primary cultures, strains of diploid cells, and transplanted lines.

Ye. F. Bocharov, S. I. Radzhabli, O. V. Sablina, and A. A. Trukhachev (USSR) reported on the effect of certain oncogenic and nononcogenic viruses on chromosomes of mammals and man. In particular they investigated chromosomal anomalies in the embryonic cells of man following their infection with adenoviruses of types 3, 5, 12, and 18, and also the virus of herpes simplex.

Postlvayt (Scotland) detected substances of the interferon type in cultures of mouse embryonic tissue which were infected with the virus of Molluscum contagiosum.

R. A. Kukayn and L. I. Nagayeva (USSR) demonstrated that the virus of Shoup papilloma produces a cytopathic effect in a culture of kidney cells from a rabbit embryo. The remaining primary cultures tested were not sensitive to this virus. In golden hamsters the papilloma virus caused tumorous growths on the cutaneous covering of the auricles, around the mouth, and the anus.

I. S. Irlin, Z. N. Tikhonova, and G. F. Smukshina (USSR) described chronic infection by the polyoma virus of transplanted kidney cells from adult mice of the A/Sn line (APO cellular line). After development of the primary cytopathic effect in the cultures there remained a small quantity of viable cells which produced the source for a new cell line, designated APOSE by the authors. The new line was highly resistant to the cytopathic effect of the polyoma virus and during numerous passages constantly yielded small amounts of this virus. All the remaining properties of cells of the initial and infected cell lines (capacity to adsorb polyoma virus, nature of growth, absence of foci of transformation, survival of mice, effectiveness of inoculation) were the same.

N. N. Dodonova, A.T. Kravchenko, A. D. Altshteyn, O. F. Sarycheva, Ye. A. Shchekochikhina, N. N. Vasilyeva, L. N. Kuborina, and Ye. M. Tseytlin (USSR) compared the biological and transforming action of 2 strains of OB40 virus (synonym of SV_{40}) which were different in their infectious properties. The two strains studied differed in the size of the plaques formed. This may have been connected with the lesser amount of viral particles escaping from cells of tissue cultures following infection with one of them (strain No 128).

In a tissue culture both strains transformed embryonic cells of mice, rats, hamsters, and man. In a culture of hamster kidney cells the transforming activity of strain No 128 was approximately 10 times greater than in strain A-426. It is interesting that the OB_{40} virus, deprived of infectious activity with hydroxylamine, still caused the transformation of cells.

Raposa (USA) presented the detailed biological characteristics of monkey adenovirus SV-20, which causes tumors in golden hamsters. This virus forms plaques in primary cultures of monkey kidneys. AT 4° it agglutinates erythrocytes of rats, rhesus monkeys, and guinea pigs, and also causes the phenomenon of hemadsorption in cells of monkey kidneys.

Rayfako (USA) presented the results of the serological investigation of more than 12 strains of human adenovirus type 12. In the neutralization reaction all of the strains studied could be divided into 2 groups. Only one type was capable of causing tumors and the transformation of hamster cells.

A. V. Frolov (USSR) discussed the strengthening of the carcinogenic activity of urethane by the virus of influenza type A2 and B. After the single administration of urethane and influenza virus to mice most often subcutaneous tumors developed, though neoplasms of the stomach, intestines, and submaxillary glands were encountered. The tumors which developed could be transplanted with cell-free filtrates.

V. S. Derkach (USSR) described the action of various enzymes on inclusion bodies which were detected in the cytoplasm of various tumorous cells. These inclusions were destroyed by trypsin and pancreatic amylase and were not destroyed by lipase.

Professor L. A. Zil'ber presented the summary of the conference on tumor viruses. He noted the doubtless successes in this area and stated that virologists had 2 missions standing before them: 1) to clear up if human tumors are caused by viruses, and 2) to determine if a carcinogen which has been introduced into an organism acts directly or does it only activate the tumor viruses which themselves cause the tumors. The great achievements of recent years in experimental virology make it possible to hope for the solution of these problems in the near future.